

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

IV. REMARKS

1. STATUS OF THE CLAIMS

Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 are pending, and stand rejected.

Claims 1, 2, 10, 11, 15-18, 25, 28, 30, 32, 34, 36, 40-44 and 50-52 are amended. Claims 3-9, 12-14, 19-21, 23, 24, 26, 29, 31, 37-39, 45, and 47 remain unchanged.

2. SUMMARY OF THE AMENDMENTS

Claims 1, 2, and 15-18 have been amended to correct references to "a group" to recite "the group." The latter term is more appropriate since each group being referred to has the appropriate antecedent basis. For example, Claim 1 defines a group of formula (a). Later reference to formula (a) in Claim 1 has been amended to recite "the group of formula (a)" instead of "a group of formula (a)."

Claims 1, 2, and 15-18 have also been amended to delete the term "linker." Accordingly, the claims now recite that attachment is to "X" rather than to "a linker," and X is now defined as having the recited formula rather than "a linker" having said formula.

Claim 25 has been amended to recite that L₁ is "attached" rather than "bonded" to X, so as to use terminology consistent with that used in Claims 1 and 2.

Claims 50 and 52 have been amended to incorporate the definitions from Claims 1 and 2 respectively. In Claim 50, the definition of L₁ has been revised since the definition in Claim 1 referred to attaching L₁ to X, which is not present in Claim 50. Accordingly, the definition of L₁ in Claim 50 refers to attaching L₁ to the hydrogen in the formula L₁-H.

Grammatical corrections have been made to Claims 1, 2, 28, 32, 34, 36, 41-43 and 51, as well as corrections so as to provide for the use of consistent terminology in the claims. For example, amending the claims to recite: "heteroaryloxy" instead of "heteraryloxy" (page 19, line 10 of the Specification); thioheteroaryloxy instead of "heteroarylthio" (page 22, lines 1-3); "halo" instead of "halogen" (page 18, line 18); "thioalkoxy" instead of "alkylthio" (page 21, line 25); "thiol" instead of "thio" (page 21, line 24); "heterocycle" instead of the term "heterocyclic" or "heterocyclyl" (see page 19, line 15 to page 20, line 2); "hydroxyl" and "carboxyl" instead of "hydroxy" and "carboxy" (page 11, lines 1-2); "carboxyalkyl" instead of "carboxylalkyl" (page 17, line 12); and "heterocyclooxy" instead of "heterocyclyloxy" (page 20, line 12).

The dependency of Claims 10, 11, 16-18, and 40-44 has been amended.

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

Claim 30 has been amended to recite that the phenyl ring is optionally substituted with 1, 2, or 3 fluoro groups. Support therefor can be found, for example, in Claim 38 and at page 76, line 1 of the Specification.

The Specification has been amended to correct typographical errors.

The amendment of pending claims should not be construed as abandonment of any originally claimed subject matter. Accordingly, the amendments made herein are without prejudice to further prosecution in a continuation, continuation-in-part, divisional or other related application. Furthermore, it is noted that the amendments to Claims 1, 2, 10, 11, 15-18, 25, 28, 30, 32, 34, 36, 40-44 and 50-52 did not narrow them. Accordingly, a full scope of equivalents is available for these claims.

No new matter has been added.

3. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement and lacking enablement.

35 U.S.C. § 112, first paragraph requires that the specification contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. Thus, this section of § 112 recites three independent and distinct requirements for the specification: the enablement requirement, the written description requirement, and the best mode requirement. The enablement and written description requirements, which are at issue here, are addressed in detail below.

The Examiner notes that substituents R_x , R^4 , R^5 , B, Z, R, R' , R'' , R^{27} , R^{36} , R^{37} , R^{46} and R^{47} , are drawn to, for example, heteroaryl [sic], heterocycloamino, heteroarylene, heterocyclene, heteroaryl, heterocyclic, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heteroaralkyl, thioheteroaryloxy, thioheterocycloxy, which are not sufficiently described or enabled in the Specification. The Examiner further argues that the examples in the Specification are drawn to the X linker and not to the moieties and their substituents.

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

The Examiner also indicates that "it is recognized that the 'A' ring has been defined as being phenyl and pyridine." Applicants wish to clarify for the record that in Claim 1, the "A" substituent is defined as being an aryl or a heteroaryl ring. Dependent Claim 2 recites that A can be phenyl or pyridyl. Thus, phenyl is a *species* of the aryl ring *genus*, rather than being a *definition* of an aryl ring. Similarly, pyridine is a *species* of the heteroaryl ring *genus*, rather than being a *definition* of a heteroaryl ring.

A. WRITTEN DESCRIPTION

35 U.S.C. § 112, first paragraph requires that the specification describe the claimed subject matter. This is referred to as the "written description" requirement, and the Examiner bears the burden of establishing a *prima facie* case to support such a rejection. See, for example, *Ex parte Sorenson*, 3 U.S.P.Q. 1462, 1463 (B.P.A.I. 1987) (citing *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976)) ("the examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in [the] specification disclosure a description of the invention defined by the claims.").

In the present case, the Examiner has alleged that certain substituents are drawn to moieties that are not sufficiently described in the Specification. Applicants submit that the terms used to describe the moieties are well understood to those skilled in the art. Determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art. That knowledge can be established by reference to patents and publications available to the public prior to the filing date of the application. For example, a brief view of the US patent Office database indicates that the term "heteroaryl" (used in the definition of R^x, R⁴, R, R', and R" in Claim 1, and of R²⁷, R³⁶, R³⁷, R⁴⁶, and R⁴⁷ in Claim 2) appears in the claims of over 500 patents issued from January 1, 1999 to the December 7, 1999 filing date of the parent of the instant application, and the term "heteroaryloxy" (used in the definition of R²⁷, R³⁶, and R³⁷ in Claim 2) appears in the claims of almost 40 patents issued over the same period. This establishes that many, if not all, of the claim terms were commonly used in patents issuing at the time the instant application was filed, thus implying a certain level of knowledge possessed by those skilled in the art.

While not all of Applicants' claim terms may appear with such frequency, the claim terms are also well defined in the Specification. The following table identifies the terms

Application No. 09/732,241
 Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
 Reply to Office Action of May 23, 2005

PATENT
 Attorney Docket No. P-095-US1
 Customer No. 27038

questioned by the Examiner, where they appear in the claims, and the location of their definitions in the Specification:

Term	Claim	Specification
heteroaryl	R^x, R^4, R, R^3, R'' (Claim 1); $R^{27}, R^{36}, R^{37}, R^{46}, R^{47}$ (Claim 2)	page 18, line 19 to page 19, line 6
heteroarylene	Z (Claim 1)	page 19, lines 11-14
heteroaralkyl	R_x, R^5 (Claim 1); R^{27}, R^{36}, R^{37} (Claim 2)	page 19, lines 7-9
heteraryloxy (amended to read heteroaryloxy)	R^{27}, R^{36}, R^{37} (Claim 2)	page 19, line 10
heteroarylthio (amended to read thioheteroaryloxy)	$R^{27}, R^{36}, R^{37}, R^{46}, R^{47}$ (Claim 2)	page 22, lines 1-3
heterocyclic and heterocyclyl (amended to read heterocycle)	R, R^3, R'' (Claim 1); $R^{27}, R^{36}, R^{37}, R^{46}, R^{47}$ (Claim 2)	page 19, line 15 to page 20, line 2
heterocyclene	Z (Claim 1)	page 20, lines 14-16
heterocycloamino and heteroarylamino	B (Claim 1)	page 21, lines 1-17; page 20, lines 17-28
heterocyclyloxy (amended to read heterocyclooxy)	R^{27}, R^{36} , and R^{37} in Claim 2	page 20, line 12
thioheterocyclooxy	R^{46}, R^{47} (Claim 2)	page 20, line 13

This table demonstrates that all of the questioned claim terms are adequately defined within the Specification. In addition, Applicants have reviewed the claims and Specification, and made corrections to further insure consistent use of chemical nomenclature. Specific examples of many of these moieties are indicated in the definitions portion of the Specification as well as being depicted structurally, for example in the listing of L_2 embodiments, spanning pages 30-75. Thus, Applicants submit that the Specification fully meets the written description requirement since the claimed invention is described therein in sufficient detail so as to establish that the inventor had possession of the claimed invention, as of the filing date of the application.

The Examiner has also alleged that the claims do not meet the written description requirement since the examples in the Specification are drawn to the X linker and not to the moieties and their substituents. Certain claims define X by a formula. For example, Claim 1 defines X as having the formula: $-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$. This formula and its components are clearly defined at page 8, lines 2-24. Other claims provide various embodiments of X, such as an "optionally substituted alkylene" in Claim 26, or the structure in Claim 30. The Specification

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

mirrors these descriptions, as well as providing embodiments in Table A on page 103 ($-(CH_2)_4-O-(CH_2)_4-$) and in Table B on page 104 ($-(CH_2)_8-$). The Specification also describes numerous compounds that can be used to form the linker (X1-X100 on pages 85-94 of the Specification) from which the structure of "X" can be easily ascertained. While the Examiner is correct that the Specification does not match up these exemplary linkers with the individual X^a , Z, Y^a , Y^b and m components, Applicants submit that one skilled in the art would recognize that the Specification does describe the invention defined by the claims.

In conclusion, Applicants assert that the Examiner has not established a *prima facie* case of lack of written description, and therefore respectfully request that the rejection of Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 under 35 U.S.C. §112, first paragraph, be withdrawn.

Should the Examiner maintain this rejection, Applicants respectfully request that the Examiner sufficiently explain why one skilled in the art would not recognize that Applicants had possession of the claimed subject matter at the time the application was filed.

B. ENABLEMENT

35 U.S.C. § 112, first paragraph requires that the specification describe the manner and process of making and using the claimed invention in such full, clear, concise, and exact terms as to enable one skilled in the art to make and use the invention. This is referred to as the "enablement requirement" and, by law, a patent application is presumptively enabled when filed. During examination, as a matter of Patent Office practice, the specification must be taken to be in compliance with the enablement requirement unless there is reason to doubt the objective truth of the statements contained therein. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971).

Thus, the Examiner has the initial burden to provide evidence to support a rejection under 35 U.S.C. §112, first paragraph. The first paragraph of 35 U.S.C. §112 requires no more than a disclosure sufficient to enable one skilled in the art to carry on the invention commensurate with the scope of the claims. Factual considerations outlined by the court in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (CAFC 1988) include: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples relating to the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

unpredictability of the art; and (8) the breadth of the claims. The Court also indicated that any determination that undue experimentation would have been needed to practice the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual consideration, including the eight factors identified above. The Examiner has failed to provide any analysis using these factors.

However, in an attempt to expedite prosecution on this matter, Applicants will address each issue to establish that the enablement requirement has been met. It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it. Applicants submit that the Specification identifies and exemplifies the L₁, X, and L₂ components of the claimed compounds of formula (I), as well as disclosing preparation of compounds of formula (I) that contain such moieties. Further, Applicants submit that one skilled in the art would be able to make any of the claimed embodiments without undue experimentation.

THE QUANTITY OF EXPERIMENTATION

The Specification provides 15 pages of general synthetic schemes illustrating how compounds of formula (I) can be prepared (pages 83-98), illustrating different schemes (pages 83, 95, and 96), exemplary functional groups and reaction conditions to provide specific linkages (Table 1, page 84), and suitable starting materials to incorporate the desired moieties (pages 85-94). Numerous embodiments of the L₁, X and L₂ components of the claimed compounds are provided in the Specification, as well as ample discussion regarding making compounds of formula (I). A total of 146 compounds were actually synthesized to guide and direct the skilled artisan in practicing the claimed invention.

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the quantity of experimentation presented in the Specification.

THE AMOUNT OF DIRECTION OR GUIDANCE PRESENTED

As noted above, the Examiner has alleged that certain substituents are drawn to moieties that are not sufficiently enabled in the Specification. First, Applicants submit that these moieties are well defined with the Specification. Second, Applicants submit that specific examples of

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

these moieties are set forth in the Specification and/or exemplified as part of an L₁, L₂ or formula (I) structure.

The term "heteroaryl" is used in reference to R^x, R⁴, R, R', and R" in Claim 1, as well as in reference to R²⁷, R³⁶, R³⁷, R⁴⁶ and R⁴⁷ in Claim 2. As noted above, this term is defined in the Specification, and specific examples are provided such as pyridyl, furyl, indoliziny, benzothienyl, and pyrrolyl (page 19, lines 4-6). At page 20, lines 3-11, numerous examples of nitrogen-containing heteroaryls are listed.

The term "heteroarylene" is used in reference to Z in Claim 1. As noted above, this term is defined in the Specification, and specific examples are provided such as 2,6-pyridylene, 2,4-pyridylene, 1,2-quinolinyne, 1,8-quinolinyne, 1,4-benzofuranylene, 2,5-pyridnylene, and 2,5-indolenyl (page 19, lines 13-14).

The term "heteroaralkyl" is used in reference to R_x and R⁵ in Claim 1, and R²⁷, R³⁶ and R³⁷ in Claim 2. As noted above, this term is defined in the Specification, and specific examples are provided such as pyridylmethyl, pyridylethyl, indolylmethyl (page 19, line 9).

The term "heteroaryloxy" is used in reference to R²⁷, R³⁶, and R³⁷ in Claim 2, as amended. The term "thioheteroaryloxy" is used in reference to R²⁷, R³⁶, R³⁷, R⁴⁶ and R⁴⁷ in Claim 2, as amended. As noted above, these terms are defined in the Specification. While no specific examples are provided as part of these definitions, there are numerous examples of "heteroaryl" groups provided in the definition section as well as illustrated in the exemplified compounds described throughout the Specification. Thus, there is ample guidance and direction as to what is intended by the terms "heteroaryloxy" and "thioheteroaryloxy."

The term "heterocycle" is used in reference to R, R', and R" in amended Claim 1, and R²⁷, R³⁶, R³⁷, R⁴⁶ and R⁴⁷ in amended Claim 2. As noted above, this term is defined in the Specification, and specific examples are provided such as morpholine and piperidinyl (page 20, line 2). At page 20, lines 3-11, numerous examples of nitrogen-containing heterocyclics are listed. In addition, the table of L₂ embodiments, spanning pages 31-75 provide numerous examples of heterocycle moieties.

The term "heterocyclene" is used in reference to Z in Claim 1. As noted above, this term is defined in the Specification, and specific examples are provided such as groups 2,6-morpholino and 2,5-morpholino (page 20, lines 15-16).

The terms "heterocycloamino" and "heteroarylamino" are used in reference to B in Claim

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

1. As noted above, these terms are defined the Specification. Specific examples are also provided. Specific examples of heterocycloamino groups are: pyrrolidino, piperidino, morpholino, piperazino, indolino, thiomorpholine, quinuclidine, 1-azabicyclo[2.2.1]heptyl, and 1-azabicyclo[3.2.1]octyl (page 21, lines 14-16). Further examples of heterocycloamino groups are set forth as formulas (j), (k), and (l) on page 27, line 24 to page 29, line 18. Specific examples of heteroaryl amino groups are: imidazole, pyrazole, benzimidazole and benzpyrazole (page 20, lines 27-28).

The term "heterocyclooxy" is used in reference to R^{27} , R^{36} , and R^{37} in Claim 2 (as amended), and the term "thioheterocyclooxy" is used in reference to R^{46} and R^{47} in Claim 2. As noted above, these terms are defined in the Specification. While no specific examples are provided as part of these definitions, there are numerous examples of "heterocyclic" groups provided in the definition section as well as illustrated in the exemplified compounds described throughout the Specification. Thus, there is ample guidance and direction as to what is intended by the terms "heterocyclooxy" and "thioheterocyclooxy."

Also as noted above, the Examiner has alleged that the claims do not meet the enablement requirement since the examples in the Specification are drawn to the X linker and not to the moieties and their substituents. The "X" component of formula (I) is described in several ways, all of which provide sufficient guidance and direction so that one skilled in the art can practice the invention. In Claim 1, X is defined as having the formula: $-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$. This formula and each individual component is defined in the Specification (page 8, lines 6-24). Applicants submit that this, alone, provides an enabling disclosure. The Specification (page 75, lines 7-8) also describes one embodiment of the "X" linker as being, for example, an alkylene group where 1-3 carbon atoms have been replaced by an oxygen atom (Claim 26). Another example of the "X" linker is set forth in the Table A on page 103: $-(CH_2)_4-O-(CH_2)_4-$. One hundred examples (X1-X100) of compounds that can be used to form various linkers are described on pages 85-94 of the Specification. One skilled in the art would readily understand what selection of X^a , Z, Y^a , Y^b , and m values would provide an alkylene group where 1-3 carbon atoms have been replaced by an oxygen atom, as well as what values would yield $-(CH_2)_4-O-(CH_2)_4-$, or structures X-X100, as well as how to synthesize such a linker. Thus, the Specification, and its description of the "X" linker, adequately teaches one skilled in the art what the invention is and how to practice it.

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

As for making the claimed compounds, the Specification sets forth several schemes as well as actual examples. Starting materials, sources and references that describe their manufacture are discussed at page 82, lines 12-22. Starting materials to create linkages are set forth as compounds X1-X100 (pages 85-94 of the Specification). Reference is also made to several journals and publications to assist one skilled in the art to practice the invention, for example: EP 747 355 and Naito et al., Chem. Pharm. Bull., 1998, 46(8), 1286 is referred to at page 95, lines 3-5 of the Specification as describing the synthesis of compounds of formula (a) where A is phenyl, pyridyl, and the like; Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992 is referred to at page 95, lines 15-17, and page 96, lines 5-6 and lines 21-23 of the Specification, as describing the reductive alkylation of amines; and WO 99/64043 is referred to at page 98, lines 2-3 of the Specification as describing methods of making the compounds of the invention using combinatorial chemistry techniques.

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the amount of direction and guidance presented in the Specification.

THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

The Specification provides 15 pages of general synthetic schemes illustrating how compounds of formula (I) can be prepared (pages 83-98), describes different schemes (page 83, page 95, and page 96), sets forth exemplary functional groups and reaction conditions to provide specific linkages (Table 1, page 84), and identifies suitable starting materials to incorporate a variety of moieties (pages 85-94).

Example 1 provides a detailed synthesis of 4-methylpiperidin-4-yl-N-(2-biphenyl)carbamate (formula (VI)), which is an exemplary "L₁-X" component of formula (I). Compounds 1-26 were then synthesized with varying L₂ groups, which were typically linked to X through the secondary non-aromatic amine of L₂. In Example 2, a different "L₁-X" component of formula (I) was prepared, designated formula (VII). Compounds 27-146 were then synthesized, with varying L₂ groups. Therefore, the Specification identifies a total of 146 specific compounds of the invention.

As long as the specification discloses at least one method for making and using the claim invention that bears a reasonable correlation to the entire scope of the claim, then the enablement

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

requirement is met M.P.E.P. § 2164.01(b). Here, Applicants have provided several schemes as well as actual examples.

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the number of working examples presented in the Specification.

THE NATURE OF THE INVENTION

M.P.E.P. § 2164.05(a) sets forth that the nature of the invention is the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The subject matter to which the claimed invention pertains is medicinal chemistry. The pharmaceutical arts is a well established field and highly educated researchers have worked, published and patented in this field for many years. Thus, this was a well developed art at the time the application was filed, and the level of skill high. The M.P.E.P. also goes on to state that the specification does not need to disclose what is well-known to those skilled in the art and "preferably omits that which is well-known to those skilled and already available to the public."

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the nature of the invention.

THE STATE OF THE PRIOR ART

The state of the art is used to determine the amount of detail that must be provided in the specification in order for it to be enabling. Thus, the state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification to meet the enablement requirement.

M.P.E.P. § 2164.03 explains that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. When a great deal is known in the prior art about the nature of the invention and the invention is in a predictable art, then less information on how to make and use the invention is required in the specification. By contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, then in order for the specification to be enabling, it must disclose more detail on how to make and use the invention.

The field of medicinal chemistry is a well established field. There are numerous texts

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

that provide instruction on the synthesis of chemical compounds, as well as treatises and on-line journals available to assist one of skill in the art with the synthesis of any given compound. Thus the state of the art is well developed.

In addition, a review of the Specification reveals that Applicants have provided sufficient disclosure to enable one skilled in the art to make and use the invention. The Specification provides 15 pages of general synthetic schemes illustrating how compounds of formula (I) can be prepared and provides several chemical schemes, as well as lists exemplary functional groups, reaction conditions to provide specific linkages, and suitable starting materials to incorporate a variety of moieties. Applicants submit that the medicinal chemistry art is relatively predictable, in that given a successful synthesis (as Applicants have done); one skilled in the art could reasonably expect to successfully make other compounds within the genus using the disclosure in the Specification and the knowledge in the general medicinal chemistry art.

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the state of the prior art.

THE RELATIVE SKILL OF THOSE IN THE ART

Medicinal chemistry is a well established field, where one skilled in the art typically possesses a graduate degree and often some post-graduate experience. There are few fields where the level of skill is higher. Therefore, in light of the high degree of skill in the art and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the relative skill of those in the art.

THE PREDICTABILITY OR UNPREDICTABILITY OF THE ART

M.P.E.P. § 2164.03 explains that the predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change, then there is a lack of predictability in the art. With respect to the amount of disclosure required in an unpredictable art, the M.P.E.P. notes that even in unpredictable arts, a disclosure of every operable species is not required. However, in cases involving unpredictable factors, such as most chemical

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

reactions, disclosure of more than a single species may be required.

In the instant case, there is ample disclosure of general synthetic schemes, exemplary functional groups, reaction conditions, suitable starting materials, as well as working examples. The synthetic routes involves chemical steps that are well understood in the art and can be carried on with a fair degree of certainty as to what product will result from a given reaction. For example, Table I (page 84 of the Specification) indicates that when a first compound having a carboxyl functional group is reacted with a second compound having an amine functional group, the resulting compound will be made up of the first compound linked to the second compound by an amide linkage. The table goes on to provide numerous such examples of reactive functional groups and resulting linkages. Further exemplifying this point are the one hundred dihydroxyl and dihalo starting materials provided that will give a variety of "X" linkers (X1-X100 on pages 85-94 of the Specification) using straight-forward chemistry. The exemplary dihydroxyl compounds can be reacted with a ligand bearing a leaving group to provide an ether bond, while the dihalo compounds can predictably be reacted with a ligand bearing an amine to form a substituted amine bond (page 85, lines 4-8); with both reactions occurring with a reasonable expectation of achieving the desired linkage. This detailed disclosure more than adequately makes up for any perceived unpredictability in the art with respect to the claimed invention.

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the application is enabling in light of the predictability of the art.

THE BREADTH OF THE CLAIMS

Turning to the M.P.E.P. for guidance as to claim breadth, M.P.E.P. § 2164.08 explains that the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claim. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The second inquiry is to determine whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

Applicants submit that the breadth of the claims is commensurate with the disclosure in the Specification. All claim terms describing the various moieties in formula (I) are defined. In

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

addition, numerous exemplary embodiments are set forth in the Specification, for example exemplary L₂ ligands are described by formulas A1-A241, A301-A439, and A5012-A590, and exemplary "X" linker moieties are illustrated by the dihydroxyl and dihalo starting materials described by formulas X1-X100. One hundred forty-six compounds were made using two different L₁ ligands, two different X linkers and an assortment of different L₂ ligands.

Applicants further submit that one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. The Specification provides numerous examples of the individual moieties that comprise formula (I), as well as significant discussion and examples of the starting materials and the chemistries needed to produce compounds of formula (I).

Therefore, in light of the foregoing discussion and the fact that the Examiner has failed to provide any analysis of this Wands factor as the basis of the enablement rejection, Applicants submit that the breadth of the claims is enabled by the disclosure in the Specification.

In conclusion, Applicants assert that the Examiner has failed to provide any evidence or reasoning to support the conclusion that the instant Specification fails to provide adequate guidance to enable one skilled in the art to practice the claimed invention, and therefore respectfully request that the rejection of Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 under 35 U.S.C. §112, first paragraph, be withdrawn.

Should the Examiner maintain this rejection, Applicants respectfully request that the Examiner provide properly reasoned and supported statements explaining Applicants' failure to comply with the enablement requirement of 35 U.S.C. §112. In addition, M.P.E.P. § 2164.08 indicates that if a rejection is made based on the view that the enablement is not commensurate in scope with the claim, the Examiner should identify the subject matter that is considered to be enabled.

4. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "linker." The Examiner's position is that there is insufficient antecedent basis for this limitation in the claim and that it is not clear what the term "linker"

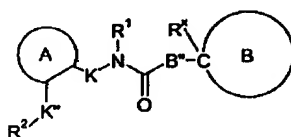
Application No. 09/732,241
 Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
 Reply to Office Action of May 23, 2005

PATENT
 Attorney Docket No. P-095-US1
 Customer No. 27038

means in the context of the claims and specification. It is Applicant's position that the term "linker" is well understood, especially in light of the definition at page 25, lines 22-23, indicating that the linker covalently attaches L₁ and L₂. However, in an attempt to expedite prosecution, Applicants have amended the claims so as to delete reference to the term "linker." The claims now recite that attachment is to "X" rather than to a "linker," and X is now defined as having a given formula rather than as "a linker" having said formula. Applicants assert that the amended language addresses the rejection and renders the claim definite under 35 U.S.C. §112, second paragraph.

Claim 1 recites the term "attach(es)." The Examiner's position is that there is insufficient antecedent basis for this limitation in the claim and that it is not clear what the term means or refers to in the claim. Claim 1 recites formula (I) as being: L₁-X-L₂, where L₁ is a group of formula (a). Originally, the "attaching" language referred to attaching formula (a) to a "linker". In Claim 1, as amended, this language now refers to attaching formula (a) to "X". Applicants submit that this amended language makes it is clear what the term "attach(es)" refers to. The other claims were similarly amended.

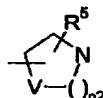
The Examiner also opines that L₁, as defined by formula (a) in Claim 1, lacks a point of attachment, thus allegedly rendering the claims indefinite. In Claim 1, as amended, L₁ is a group of formula (a):



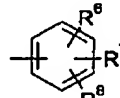
R² can be Het (which can attach the group of formula (a) to X) or the formula (i), (ii), and (iii):



(i)



(ii)



(iii)

where R³, R⁵, R⁶, R⁷, or R⁸ can be a covalent bond attaching formula (a) to X. B is heterocycloamino or heteroaryl amino, which can attach formula (a) to X. The claim also recites that at least one of these Het, R³, R⁵, R⁶, R⁷, R⁸, heterocycloamino, or heteroaryl amino groups attaches formula (a) to X. Applicants submit that the language of Claim 1 is definite because various components of the L₁ moiety are recited as being able to attach the moiety to the X

Application No. 09/732,241
Amendment Under 37 C.F.R. § 1.111 dated June 17, 2005
Reply to Office Action of May 23, 2005

PATENT
Attorney Docket No. P-095-US1
Customer No. 27038

moiety.

In conclusion, Applicants submit that the claims, as amended, meet the definiteness requirement, and therefore respectfully request that the rejection of Claims 1-21, 23-26, 28-32, 34, 36-45, 47 and 50-52 under 35 U.S.C. §112, second paragraph, be withdrawn.

5. THE INFORMATION DISCLOSURE STATEMENT

Applicants again wish to bring to the Examiner's attention that a Supplemental Information Disclosure Statement (IDS) was mailed for this application on August 22, 2002. Copies of the references, the Form 1449 and the appropriate fee were submitted at that time. The Supplemental IDS was entered into the PAIR System on August 29, 2002. To date, Applicants have not received an Examiner-initialed copy of the Form 1449. Applicants respectfully request that the Examiner consider the information provided in the Supplemental IDS and return an initialed copy of the Form 1449 to Applicants. A copy of the Form 1449 is enclosed for the Examiner's convenience.

V. CONCLUSION

The above arguments and amendments to the Specification and Claims are submitted for the purpose of facilitating allowance of the Claims and a sincere effort has been made to place this application in condition for allowance. An early notice of allowance is earnestly requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney for Applicants at (650) 808-4010.

Respectfully submitted,
THERAVANCE, INC.

Date: June 17, 2005

By: Shelley Eberle
Shelley Eberle
Reg. No. 31,411
Direct Telephone (650) 808-4010

THERAVANCE, INC.
901 Gateway Boulevard
South San Francisco, CA 94080
Telephone: (650) 808-6000
Facsimile: (650)-808-6078